

# **Patient-Centric Observation and Dose History-Driven Differentiated Care: Technologies, Evidence, Implementation**

ADHERENCE TECHNOLOGIES FOR LOW-RESOURCE SETTINGS: IMPROVING LINKAGE TO AND RETENTION IN CARE FROM TREATMENT INITIATION TO CURE

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# AGENDA

- The Intervention
- The Technologies
- The Evidence Base
- Implementation
- Conclusion

# THE PROBLEM WE'RE WORKING TO SOLVE

## PROBLEM

- Even following proper diagnosis and treatment initiation, curative treatment completion remains problematic.
- There are myriad challenges to TB treatment adherence/persistence.
- The traditional response, facility-based witnessed dosing (i) is less frequently practiced, (ii) is highly resource intensive, and (iii) may create barriers to linkage and retention in care.

## EVIDENCE

Recent studies in India indicate that the patients who faced the most difficulty in accessing and completing DOTS (due to travel costs, job disruption, etc.) were the ones most vulnerable to the disease.

Patients seeking/obtaining care in the private sector and an increasingly large percentage of public sector patients are self-administering their medications and their dosing is not being observed.

Large (4500 patients) study in China showed average adherence for self-administering patients is approximately 70%. Data from India suggests that private sector adherence is even lower.



# SOLUTION OBJECTIVES

## **IMPROVED PERSISTENCY OF TREATMENT**

Patients taking drugs more regularly and more likely to continue treatment. More patient-friendly approach to monitoring while giving providers information to counsel patients to remain on treatment.

## **MORE EFFICIENT USE OF RESOURCES**

Lower cost to monitor/manage patients during treatment. Adherence data helps providers identify high risk patients and differentially invest resources to improve persistency on treatment.



**BENEFITS OF  
NEW  
ADHERENCE  
TECHNOLOGY-  
ENABLED  
CARE**

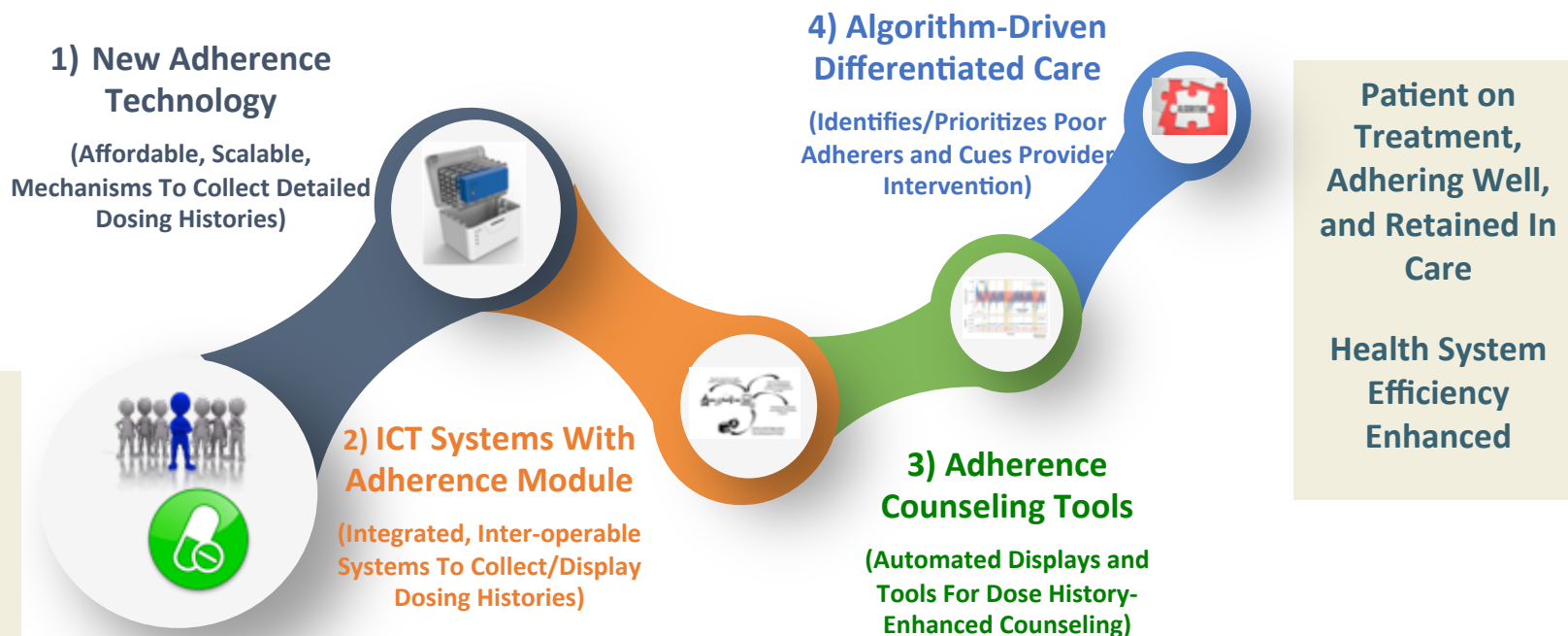
## **BETTER HEALTH OUTCOMES**

Improved treatment completion and adherence leads to better health outcomes (being confirmed in China study); potentially limiting the development of resistance and reducing transmission.

## **BETTER DEVELOPMENT DATA**

Detailed adherence data helps build understanding of why new drug regimens succeed or fail in clinical practice; helping to plan the development of new regimens and their TPP's

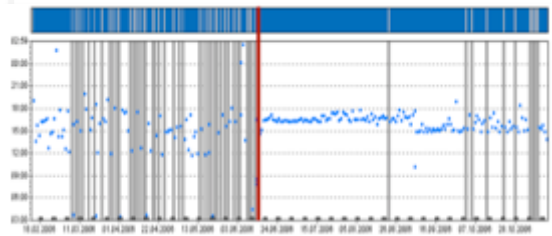
# OUR APPROACH: PATIENT-CENTRIC OBSERVATION AND DIFFERENTIATED CARE



# THE IMPACT WE EXPECT

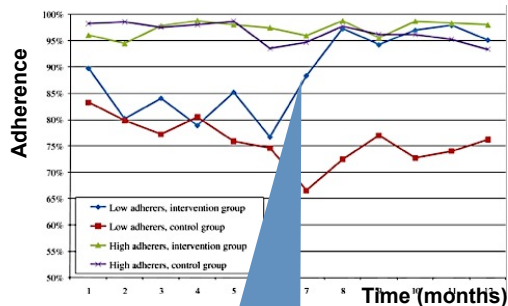
ACCURATE, DETAILED DOSING  
HISTORIES...

Patient's dosing history



... HELP IMPROVE ADHERENCE BY  
IDENTIFYING HIGH RISK PATIENTS AND  
ENABLING IMPACTFUL COUNSELING

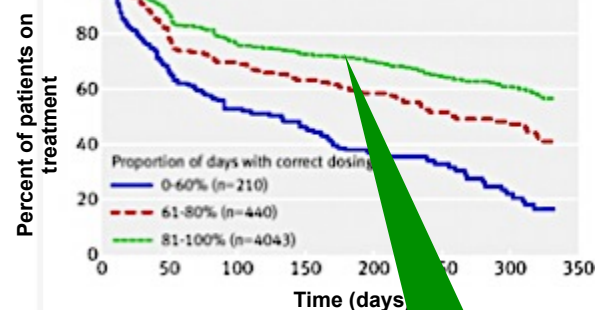
Patient's adherence over time



Targeted EDM-enabled  
counseling improved low  
adherer's adherence rates  
by >20%

... WHICH LEADS TO GREATER  
PERSISTENCY ON TREATMENT

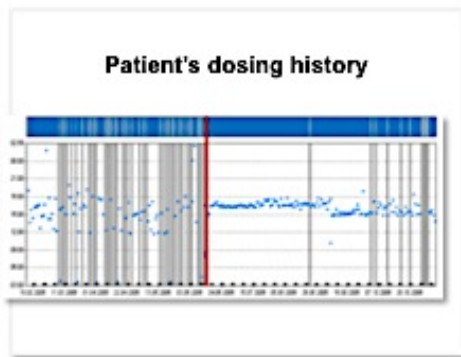
Patient cohort persistency on  
treatment over time



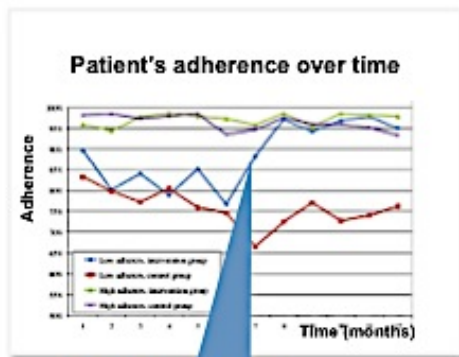
More adherent  
patients also persist  
on therapy MUCH  
longer

# CRITICAL ENABLER . . .

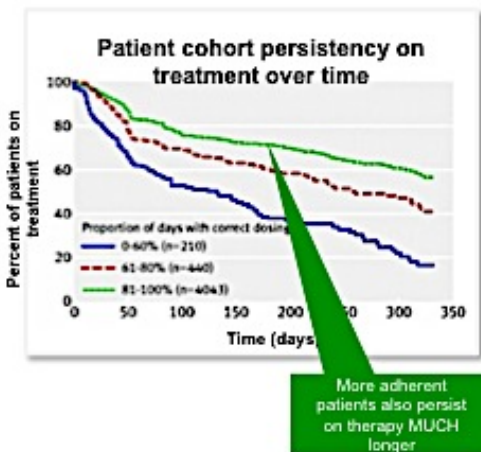
ACCURATE, DETAILED DOSING HISTORIES...



... HELP IMPROVE ADHERENCE BY IDENTIFYING HIGH RISK PATIENTS AND ENABLING IMPACTFUL COUNSELING



... WHICH LEADS TO GREATER PERSISTENCY ON TREATMENT



**CRITICAL ENABLER: ACCURATE, DETAILED DOSING HISTORIES . . . COMPILED IN A MANNER THAT IS AFFORDABLE, SCALABLE, AND ACCEPTABLE TO PATIENTS AND PROVIDERS**

# AGENDA

- The Intervention

- The Technologies

- The Evidence Base

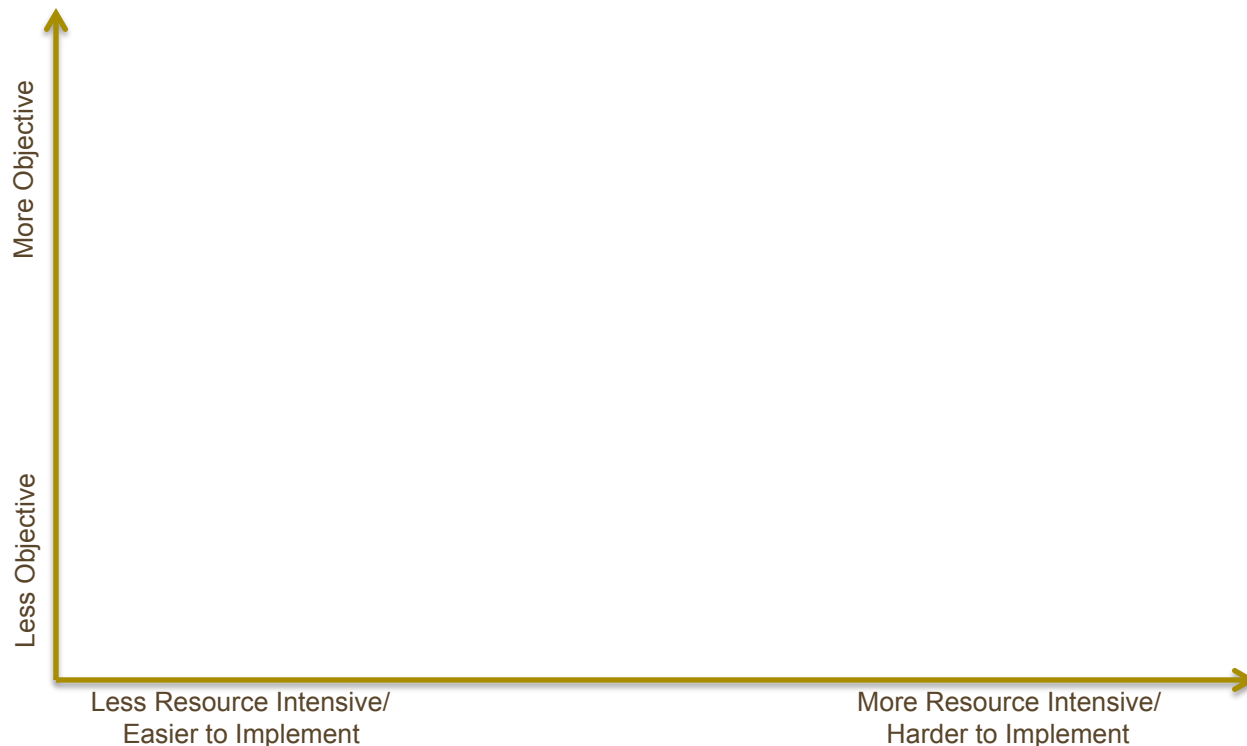
- Implementation

- Conclusion



# DOSING MEASUREMENT METHODS

## Our Framework\* For Evaluation Of Adherence Assessment Measures



### Evaluative Criteria

- **More objective/less objective:**
  - Bias or potential bias in adherence measurement
- **More resource intensive/harder to implement:**
  - Affordability
  - Patient burden
  - Cultural appropriateness
  - Technology/supply chain fit



Sparse  
Sampling



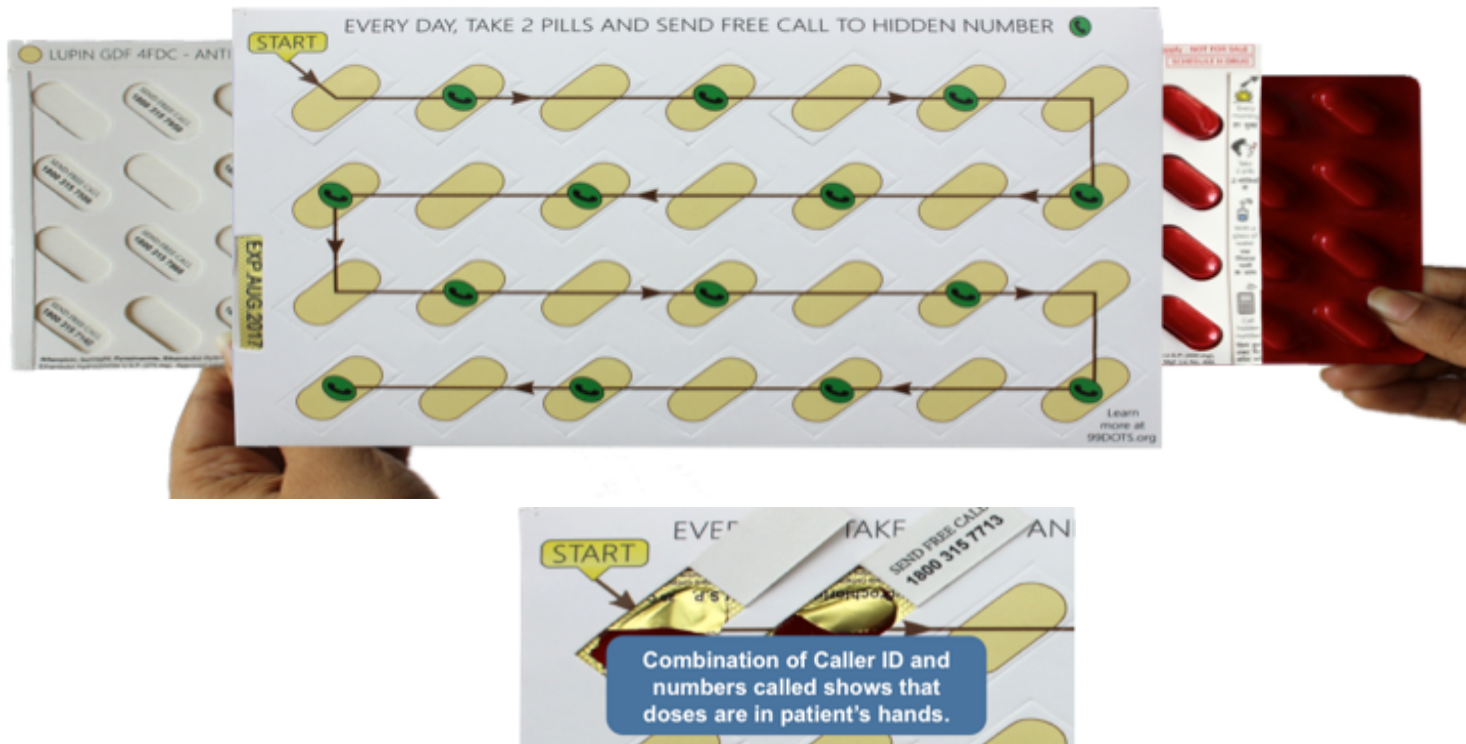
Rich  
Sampling

“Rich Sampling” refers to capture of daily, detailed dosing history.

- NOTE – specific evidence-based evaluative criteria for dose monitoring approaches are review below. This framework is used to summarize the results of that more detailed evaluation

# THE 99DOTS SOLUTION

Chosen By India's CTD To Facilitate The Shift To Daily-Dosed FDCs



# KEY FEATURES OF 99DOTS

- Calls are completely **free** for patients and can be made from any phone – mobile, land line, shared.
- Any call from a registered patient number is marked as a dose taken (personal, shared, land line).
- Numbers are not unique, but appear in an unpredictable sequence – ensures “**pill-in-hand**” **adherence**.
- When patients call, they hear “Thank you.”
- Calls **immediately** show up in the dashboard as taken doses.
- **Automatic alerts** and reminders to patients and supervisors for non-adherent patients.
- Adherence records available to field staff, medical officers, district staff and all other stakeholders in the program – via mobile devices.
- **Open source** ICT system – integratable with national health systems (India) and with other adherence monitors (MERM).

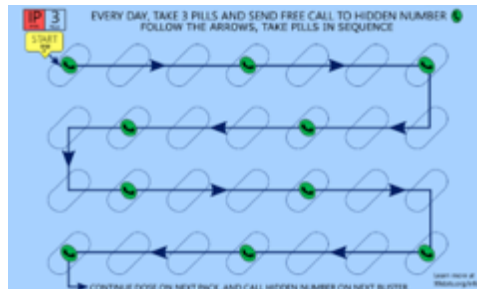


Two of your  
patients have  
missed doses  
Raj (979XXXXXX)  
& Om (812XXXXXX)

# IMPROVED DOSING INSTRUCTIONS AND REDUCED RISK OF DISPENSING ERROR



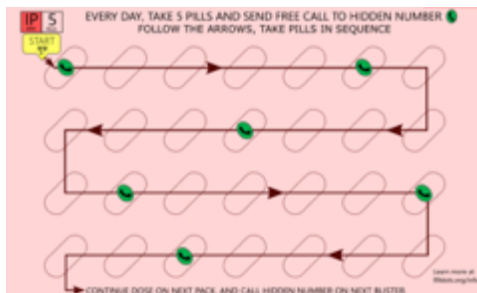
2 pills / day



3 pills / day



4 pills / day



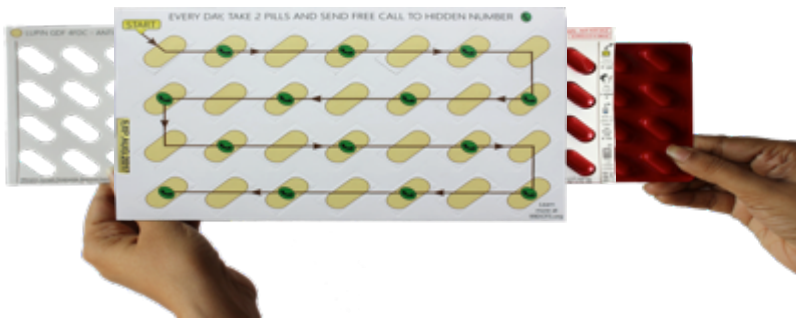
5 pills / day



Envelopes Also Clarify Phase And Weight Band



# 99DOTS: SUMMARY



## Advantages

- Affordability – about \$3 for 6 months
- Easily integrated into existing drug manufacturer supply chain
- Suitable for multiple dosing and package formats
- Assistance with dosing instruction and reduction of dispensing error
- Accurate (high level of assurance that “pill in hand”)
- Open source ICT -- proven ability to integrate with national ICT systems and other monitoring technologies

## Challenges / Questions

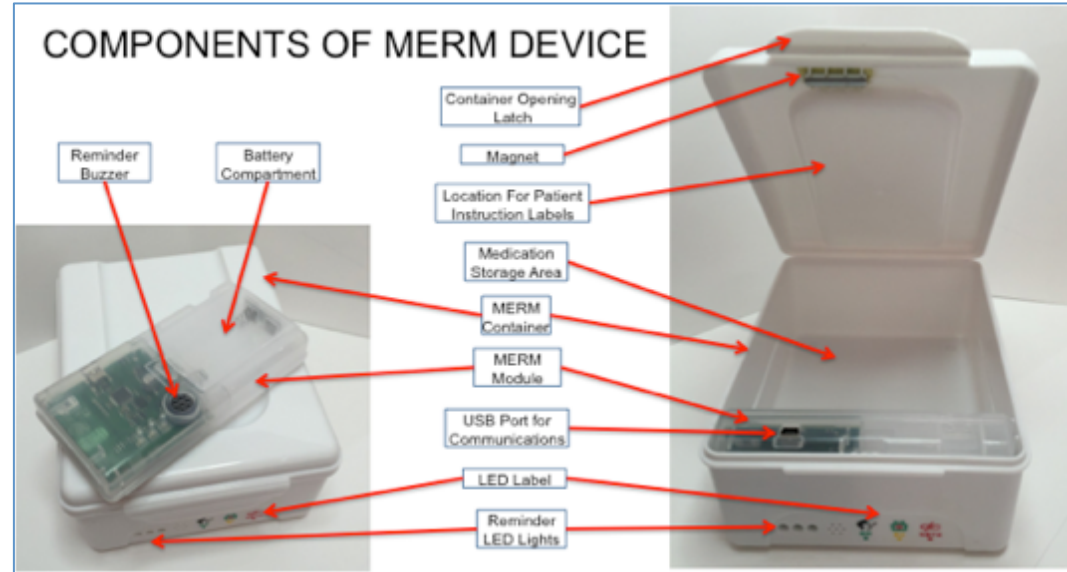
- Will patients accept (or be adequately incented to accept) the “burden” of calling with every dose?
- Reach -- borrowed phones and related access issues
- Challenges with access/availability to toll free lines

## Status (Demo, Pilot, Scale-up in Resource-Limited Settings)

- India: Deploying 99DOTS for all TB/HIV patients (45,000)
- India: Mumbai RNTCP deploying 99DOTS for all 30,000 patients
- India: Pilots underway March in PPIA Sites in Patna and Mumbai
- India: Preliminary plans to scale-up 99DOTS to 5 additional states with daily FDC (additional 250,000 patients)
- Myanmar: Pilot (10,000 patients) underway with PSI
- Ethiopia: small pilot planned in 2017

# MEDICATION EVENT REMINDER-MONITOR

- Generates accurate detailed dosing histories.
- Two versions – “real time” or store data for periodic download.
- Modular design – mass-produced “modules” and customized, inexpensive (plastic or corrugated) containers.
- Powered by **standard, disposable batteries** (6 month battery life) or rechargeable lithium batteries.
- Fits wide range of blistered medications. Large “**billboard**” for patient instructions.
- Separate audible and visible reminders of **both dosing and refill**.
- Registers daily “heartbeat” – confirming operational status in absence of dosing event.
- **Affordable**: Basic (\$7 per patient), Real-time (\$10 per patient). Highly re-usable.



**Low Patient Burden** Electronic Dose Monitor Designed Specifically For Clinical Practice Use In Resource-Limited Settings

# MERM: SUMMARY



## Advantages

- \$7 per patient for “basic” version, \$10 per patient for “real time”
- Low patient burden
- Easily integrated into existing drug manufacturer supply chain
- Suitable for multiple dosing and package formats
- Assistance with dosing/patient instruction. Refill reminder
- Integrated with 99DOTS’ open source ICT system
- Manufacturing localized in China and in Africa
- Leverages established Wisepill technology with clear path to open access

## Challenges / Questions

- Patients who travel or are migrant laborers
- Patients/locations where stigma is a significant factor
- Will there be issues of theft or use of container for other purposes?
- Will space issues (relating to inventory/storage) be a problem?

## Status (Demo, Pilot, Scale-up in Resource-Limited Settings)

- China: 2nd large (3000 patient) RCT (health outcomes, cost-effectiveness) underway with China CDC
- China: Scaling up 3 provinces at a time (45,000 patients per year). RFP issued January 22, 2017
- India: Mumbai RNTCP deploying to 2500 patients in Q3, 2017
- India: Pilots (100 patients) underway March in PPIA Sites in Patna and Mumbai
- Africa: Large (3500 patient) RCT underway in South Africa, Ethiopia, and Mozambique



# EMBRYYO BOXRx: SUMMARY



## Advantages

- Low patient burden
- Pill-specific accuracy
- Provides dosing cues/assistance
- Detailed dosing histories compiled
- Consistent/Integratable with existing supply chain

## Challenges / Questions

- Can affordability and scalability be achieved?
- Any remaining health issues regarding conductive inks?
- For existing regimens, do we need this level of pill-specific accuracy?
- How burdensome on HCW/pharmacists is the “loading” process?

## Status (Demo, Pilot, Scale-up in Resource-Limited Settings)

- India: Small (30 patient) pilot commenced late, 2016.





# “VALIDATED” (AI-ASSISTED) V-DOT: SUMMARY



## Advantages

- Should be highly accurate
- Facilitates patient-centric observation
- When technology penetration achieved, could be affordable and scalable
- May favorably resolve issues around patient willingness to “broadcast” and back-end record falsification
- Suitable for multiple dosing and package formats
- Fits/consistent with existing DOTS mindset/approach

## Challenges / Questions

- Smartphone penetration in resource-limited settings still low
- High patient burden – will patients persist?
- Will solution present cognitive challenges for target population?
- Is global health/resource-limited settings an area of interest for this AIcure?

## Status (Demo, Pilot, Scale-up in Resource-Limited Settings)

# INGESTIBLE SENSORS: SUMMARY



## Advantages

- Pill-specific accuracy – ideal for poly-pharmacy applications such as MDR-TB, TB/HIV
- Manufacturing issues favorably resolved and scalable in US/ Europe
- Facilitates patient-centric observation
- Fits with any SOD medication, including TB

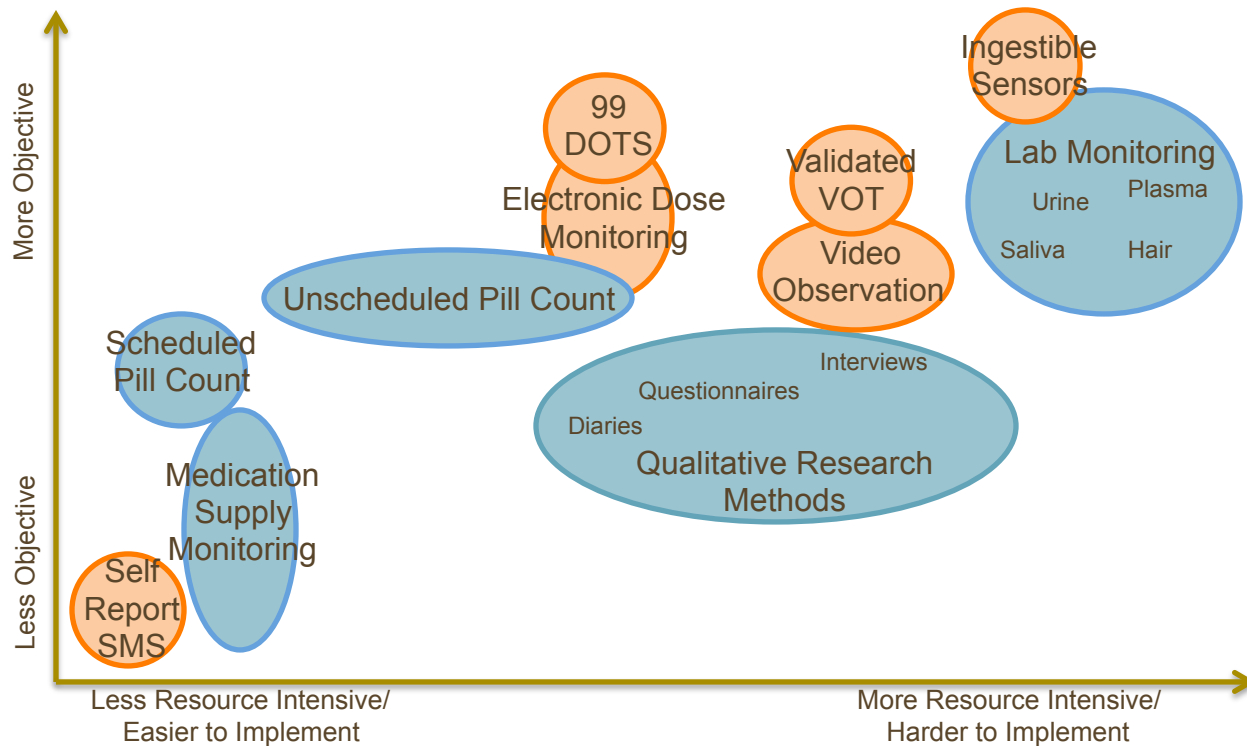
## Challenges / Questions

- Current data collection/transmission approaches highly burdensome on patients (patch)
- Currently, very expensive
- Is global health an area of interest to these providers
- Is solution as currently designed feasible given technology infrastructure in resource-limited settings

## Status (Demo, Pilot, Scale-up in Resource-Limited Settings)

# DOSING MEASUREMENT METHODS: OUR SUMMARY

Comparison Of Adherence Assessment Measures According To Their Degree of Objectivity and Ease Of Implementation In Resource-Limited Settings



## Evaluative Criteria

- **More objective/less objective:**
  - Bias or potential bias in adherence measurement
- **More resource intensive/harder to implement:**
  - Affordability
  - Patient burden
  - Cultural appropriateness
  - Technology/infrastructure fit



Sparse Sampling



Rich Sampling

"Rich Sampling" refers to capture of daily, detailed dosing history.

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# TO EVALUATE DIFFERENT TECHNOLOGIES, WE'VE DEVELOPED CRITERIA ACROSS 7 DIMENSIONS

Evaluative criteria	Description
<b>Feasibility</b>	<ul style="list-style-type: none"><li>Relative ease of implementation and operation of the technology within existing health systems, technology infrastructure, and supply chains.</li></ul>
<b>Acceptance / Burden</b>	<ul style="list-style-type: none"><li>Relative satisfaction of patients and providers with the technology.</li><li>Should include an understanding of (i) cultural or other barriers to uptake (e.g. VDOT for women/ girls), (ii) how this relative satisfaction changes over time, and (iii) how this burden affects both uptake and persistence with respect to the technology.</li></ul>
<b>Accuracy</b>	<ul style="list-style-type: none"><li>For monitoring technologies, the extent to which the technology's "event" (e.g., self-reported medication ingestion) is correlated with actual event (e.g., medication ingestion).</li></ul>
<b>Effectiveness</b>	<ul style="list-style-type: none"><li>Extent to which the technology is able to generate or elicit the intended action, behavior, or event (e.g., improvement in average adherence).</li><li>Should include information on the extent to which the effect persists over time.</li><li>Ultimate "effect" to be evaluated would be actual health outcomes (e.g. current China RCT)</li></ul>
<b>Affordability</b>	<ul style="list-style-type: none"><li>The total cost of the technology as implemented and used by patients/providers – in relation to (i) cost of treatment regimens, and (ii) total cost of treatment.</li></ul>
<b>Cost Effectiveness</b>	<ul style="list-style-type: none"><li>An assessment of cost-effectiveness/comparative cost-effectiveness (mean and incremental costs per death and DALY averted) of the proposed technology-enabled intervention versus standard of care in the relevant context, i.e., disease burden, budget/costs of the resource-limited setting.</li></ul>
<b>Available TPP</b>	<ul style="list-style-type: none"><li>Availability of a WHO TPP for the product/device.</li></ul>

# EXAMPLE: EVIDENCE BASE (HIGH BURDEN, RESOURCE-LIMITED SETTINGS ONLY)\* FOR THE MERM DEVICE

Evaluative criteria	Current state
Feasibility	<ul style="list-style-type: none"> <li>Formal usability assessment conducted (432 patients) in 2012. <i>Published -- Chin J Antituberculosis. 2012; 34:419–424 and - Liu et al, PLoS Medicine (2015)</i></li> <li>RFP issued January, 2017, for deployment across 3 provinces (75,000 patients) as standard of care.</li> </ul>
Acceptance	<ul style="list-style-type: none"> <li>Formal usability study (50 patients, 10 providers) conducted in 2016. <i>Manuscript in review (Terry Blaschke, Sabina deGeest).</i></li> </ul>
Accuracy	<ul style="list-style-type: none"> <li>432 patient study in china compared monitor records with random urine tests. <i>Published -- China J Antituberculosis. 2012;34:419–424.</i></li> </ul>
Effectiveness	<ul style="list-style-type: none"> <li>Adherence effect demonstrated in 4500 patient RCT. <i>Published -- Liu et al, PLoS Medicine (2015)</i></li> <li>Health outcomes-oriented RCT in process. Xiaoqiu Liu (China CDC) Principal investigator. 3800 patients, 24 clusters. <i>Trial Registry -- <a href="http://www.isrctn.com/ISRCTN35812455">http://www.isrctn.com/ISRCTN35812455</a></i></li> </ul>
Affordability	<ul style="list-style-type: none"> <li>Total device costs (assuming 1 re-use) \$5 per patient for “basic” version and \$10 per patient for “real time” version. 6 month DS-TB medication cost approximately \$20 per patient.</li> </ul>
Cost-Effectiveness	<ul style="list-style-type: none"> <li>In Process: Anna Vassal (LSH&amp;TM) Principal Investigator. In connection with Current RCT. <i>Trial Registry -- <a href="http://www.isrctn.com/ISRCTN35812455">http://www.isrctn.com/ISRCTN35812455</a></i></li> </ul>
Available TPP	<ul style="list-style-type: none"> <li>No</li> </ul>

\* MERM has been designed as an affordable, TB-appropriate MEMS. More than 600 published studies have used or evaluated MEMS. “MEMS is currently regarded as the gold standard to measure adherence.” – Bulletin of WHO, 2011

# OUR ASSESSMENT: EVIDENCE/SUPPORT IN HIGH BURDEN, RESOURCE-LIMITED SETTINGS

Evaluative criteria	99DOTS	MERM	EMBRYYO	VDOT	Validated/AI VDOT	Ingestible Sensors
<b>Feasibility</b>	Satisfactory data India, Myanmar Abstract Published	Satisfactory data China Published. Non-RCT	In process Non-RCT	Satisfactory data (?) Kenya – 13 patients Published. Non-RCT	Not tested in high burden countries	Not tested in high burden countries
<b>Acceptance / Burden</b>	Satisfactory data India, Myanmar Abstract Published	Satisfactory data China (India, 2017) In Review. Non-RCT	In process Non-RCT	Not yet tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
<b>Accuracy</b>	In process with NIRT 600 patients -- India. Non-RCT	Satisfactory data China Published. Non-RCT	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
<b>Effectiveness</b>	Planned - India Retrospective Study Non-RCT	Satisfactory data China Published --RCT	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
<b>Affordability</b>	Satisfactory data India, Myanmar	Satisfactory data China	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
<b>Cost Effectiveness</b>	In process India Non-RCT	In process China, India RCT	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries	Not tested in high burden countries
<b>Available TPP</b>	No	Yes (But BMGF Developed, Not WHO)	No	Yes (WHO Developed/ Endorsed)	No	No



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# IMPLEMENTATION: MUMBAI RNTCP (30,000 PATIENTS)



Notification of new patients



New patient Raj  
(740XXXXXX)  
enrolled,  
Yelahanka district

Alerts to field staff



Two of your  
patients have  
missed doses  
Raj (979XXXXXX)  
& Om (812XXXXXX)

FDCs and  
99DOTS  
Envelopes  
To State  
Drug Store

FDCs  
Wrapped In  
99DOTS  
Envelopes  
and Shipped  
to Centers

Patients  
Issued 28  
Days Of  
99DOTS-  
Wrapped  
Medication

Patients  
Registered  
On 99DOTS/  
eNikshay (All  
Phones –  
Mobile,  
Shared,  
Land Line)

TBHV  
Notified Of  
New Patient  
Assigned To  
Him/Her Via  
SMS

Patients  
Receive  
Daily SMS  
Reminders,

Patients  
Take  
Medications,  
Call Random  
Toll Free  
Number.  
Response:  
"Thank You"

Patient Calls  
Populate  
Adherence  
Dashboard.

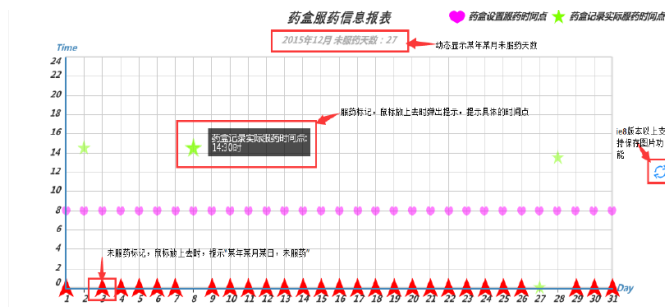
TBHV  
Receives  
Twice  
Weekly SMS  
With  
"Prioritized"  
Patients

TBHV  
Contacts/  
Visit  
"Prioritized"  
Patients For  
Counseling

Adherence  
Dashboard  
(Calendar)  
Used For  
Enhanced  
Counseling

REFILL

# IMPLEMENTATION: EMERGING NATIONAL STANDARD OF CARE IN CHINA (45,000 PATIENTS, 3 PROVINCES/YEAR)



All events – from issuance of the MERM, to enhanced counseling, to differentiated care – managed through “national” adherence/patient management system with which the MERM is fully-integrated.



FDCs and MERMS Shipped To Provincial Drug Store

FDCs Inserted Into MERM And Shipped to Hospitals/ Treatment Centers

MERM Registered To Patient, Daily Dosing Refill Alerts Set

MERM and Medications Given To Patient

Dosing Reminders (Visual and Audible) (3X)

Patient Opens MERM, Takes Medication

Dosing Event and “Heartbeat” Recorded

Patient Brings MERM or MERM Module On Refill Visit

MERM Data Downloaded and Adherence Dashboard Populated

Patient Is “Prioritized” Based On Dosing History

Provider Counsels Patient Using Patient’s Adherence Calendar

Refill Medications Inserted Into MERM.

Daily Dosing And Refill Alerts Reset (If Required)

# WHAT DO WE NEED TO DO TO BEGIN SCALING ADHERENCE TECHNOLOGIES/DIFFERENTIATED CARE ELSEWHERE?

IMPLEMENTATION KIT			
EVIDENCE BASE	TRAINING MATERIALS	ICT SYSTEM SOLUTION	PROCUREMENT
<p><i>Why this works</i></p> <ul style="list-style-type: none"> <li>• Succinct NTP-oriented summary of supporting evidence for proven technologies and dose history-driven differentiated care</li> </ul>	<p><i>How to implement</i></p> <ul style="list-style-type: none"> <li>• Leverage existing, proven training materials developed in collaboration with India RNTCP and China CDC</li> </ul>	<p><i>How to integrate it</i></p> <ul style="list-style-type: none"> <li>• Leverage 99DOTS “open source” ICT system</li> <li>• Leverage learning from eNikshay and China adherence module development</li> </ul>	<p><i>How to order it</i></p> <ul style="list-style-type: none"> <li>• Investigate feasibility and appropriateness of including proven adherence technologies in GDF product catalogue</li> </ul>

AWARENESS PLAN	
GLOBAL CAMPAIGN	IMPLEMENTERS WORK GROUP
<p><i>Getting the word out</i></p> <ul style="list-style-type: none"> <li>• Knowledge repository</li> <li>• Insight articles: peer to peer oriented</li> <li>• Social media support</li> <li>• In country consultations, e.g. India Delhi Consultation</li> </ul>	<p><i>How to help others get started</i></p> <ul style="list-style-type: none"> <li>• Peer-to-peer “user group” facilitated by WHO, BMGF, GDF</li> <li>• Current implementers and potential implementers</li> <li>• Sharing best practices/lessons learned</li> </ul>

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# CONCLUSION

- Given:
  - The Urgent Need For More Patient-Centric Alternatives To Witnessed Dosing,
  - The Feasibility and Acceptability Of These Approaches,
  - The Availability Of Open Source, Highly Integratable ICT Systems, and
  - The Significant Evidence Base And Practical, Large-Scale Experience Coming Out Of India and China
- Can't We Pick Up The Pace -- Proceeding More Aggressively With Pilots, Demos, Scale-Up In Other High Burden Regions?